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PHYSICAL PERFORMANCE FOLLOWING INHALATION OF GB [U]

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Porton Technical Paper No. 855
Copy No. 71
Date May 1963

ICAL PERFORMANCE FOLLOWING INHALATION OF GB

by

R.J. Shephard

SUMMARY

1. "Maximal" work tests have been carried out on 20 subjects, and sub-maximal work tests on a further 20 subjects, using an electrically braked bicycle ergometer.

2. Following the inhalation of GB (nominal dose 5 µg/kg) there was a small decrease in "maximal" rate of working relative to control days; following the inhalation of isopropanol, there was a small increase in the rate of working relative to control days. The difference between "test" and "control" series was of marginal significance ($0.05 < P < 0.1$), and could be explained entirely in terms of increased work of breathing.

3. Sub-maximal work tests showed an increase of oxygen consumption following inhalation of isopropanol. This again could be explained in terms of an increase in the work of breathing. The "test" series showed no increase of ventilation following inhalation of GB, implying that the increase in O_2 consumption was achieved by an increased efficiency of gas transfer in the lungs; no change of pulse rate, rise of body temperature, respiratory rate, tidal volume, respiratory quotient, or ventilatory equivalent for oxygen was observed following administration of GB.

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The group inhaling isopropanol showed a significant increase of extraventilation in the 15 min following exercise on the test day; this response was not shown by those inhaling GB.

4. Local symptoms of GB inhalation were unnoticed during vigorous exercise.

(Sgd.) C. Lovatt Evans,
Head, Physiology Section.

(Sgd.) W.S.S. Ladell,
Assistant Director (Medical).

RJS/DG

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PHYSICAL PERFORMANCE FOLLOWING INHALATION OF GB

by

R.J. Shephard

INTRODUCTION

No significant change of circulatory (1,2) or psychomotor (3) parameters can be detected in resting man following exposure to moderate single breath doses of GB (nominal 5 µg/kg), and it seems established that the effects of GB are restricted under these conditions to (a) a modest and rather transient local action on the respiratory tract (4,5), and (b) an inhibition of esterases in the blood stream (4). The extent to which these responses to GB are modified by exercise is less certain. Subjects have commented following single breath inhalations of GB that respiratory embarrassment might cause difficulty in running (4), and there have also been reports of vomiting in subjects who had exercised following relatively heavy contamination of the skin (300 mg) with liquid GB (6).

In the present experimental work, "maximal" and sub-maximal tests were carried out on the bicycle ergometer in the period immediately subsequent to a single-breath oral inhalation of GB (nominal dose 5 µg/kg), in an attempt to define what effect if any such a dose of GB might have on the rate of working, and on various parameters of ventilatory and cardiac performance during exercise.

METHODS

Subjects and experimental plan

The subjects, aged 18-31 yr, were chosen from the volunteers coming to Porton after a rigorous medical examination and P-A chest radiograph to exclude any men with possible pulmonary diseases. Blood samples were taken for cholinesterase estimation, and no man whose red cell or plasma cholinesterase was below "normal limits" was used as a subject.

Twenty men performed the maximal exercise test daily for five successive days. Immediately before the ride on Day 3, half of them were given a single-breath of GB vapour in an air/isopropanol vapour mixture (4), and the other 10 men took a single breath of the air/isopropanol vapour alone. A further twenty subjects carried out sub-maximal tests thrice daily for ten successive days. On the third day of the second week (Day 8), half were given GB and half the innocuous vapour as in the maximal exercise tests.

Exercise tests

An electrically-braked bicycle ergometer was used in all tests. Details of the apparatus and calibration curves are given in an earlier report (7).

(a) "Maximal" exercise. After a 15 min rest period, subjects were instructed to ride the bicycle as fast as they were able for a 5 min period. During this period, the men were continually encouraged to keep up their effort. Most subjects maintained a pedal speed of 45-60 r.p.m.; on a normally geared wheel bicycle, 45 r.p.m. would correspond to a roadspeed of about 10 m.p.h., maintained up the "steep hill" provided by the external load.

The average rate of working (watts) was noted each day, and on day 5 the expired air was collected in a Douglas bag for estimation of respiratory minute volume and carbon dioxide output over the period $2\frac{1}{2}$ - $4\frac{1}{2}$ min from the beginning of the exercise.

(b) Sub-maximal exercise. After a 15 min rest period, a constant rate of working of 125 watts (746 kg.m/min* and about 80% of "maximum" for these subjects) was maintained for 15 min, and subjects were followed for a further 15 min during the recovery period.

At the first run of each day, measurement was made of respiratory minute volume by dry gas meter (readings being obtained at half minute intervals throughout the 45 min period), pulse rate (before, 0, 1, 2, 3, 4, 5 and 15 min after exercise), and rectal temperature (before, 0 and 15 min after exercise). On Days 1, 5, 7, 8 and 9, oxygen consumption, CO_2 output, and respiratory rate were also measured during the last minute of exercise.

GB administration and Cholinesterase depression

For the "maximal" exercise tests, GB was administered by the standard single-breath technique (4). At the time of these tests, the weather was cold, and some difficulty was encountered with condensation of vapour in the tonometer. The cholinesterase depressions (red cell 18.3 ± 12.7%, plasma 14.6 ± 7.3%) suggest that not more than about a half of the nominal dose of 5 µg/kg was actually inhaled. The technique of GB administration was modified for the sub-maximal exercise tests by (a) keeping the tonometer warmed on a radiator until the moment of inhalation, and (b) asking the subjects to take several deep breaths from the tonometer until they were no longer able to notice any taste in the mixture. With the modified procedure, cholinesterase depressions (red cell 35.3 ± 7.8%, plasma 19.2 ± 7.2%) were a little greater than previously reported (4); it is probable that some 80% of the nominal dose was retained in the body.

"Control" inhalation

The "control" mixture contained the same volume of isopropanol vapour (~70 µl.) to that present in the tonometers containing GB vapour.

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* 1 watt = 5.97 kg.m/min = 44.2 ft.pd/min.

RESULTS

1. "Maximal" exercise tests

(a) "Control" values. On the first day of testing, subjects were able to work at an average rate of 141-183 watts (842-1092 kg.m/min) over the 5 min period (Table 1). All subjects thought that activity had been limited mainly by aching or tiredness of the leg muscles; about half of the subjects felt that shortness of breath had also been a limiting factor, and one man (19) felt "sick" towards the end of his test. The best performer (5) had been a club cyclist; the remaining subjects had no special experience as cyclists.

There was no significant improvement of "maximum" effort with repetition of the test, although several subjects commented that the ride seemed easier on the second and subsequent days. "Control" values for Day 3 have thus been calculated as the mean of results for Days 2 and 4.

(b) Effect of GB. In 7/10 subjects when given GB (Day 3), the rate of working was less than on the previous and succeeding days. However, the mean loss of working capacity for the group (-2.3 ± 1.8 watts) was small, and not statistically significant. The mean performance of the control subjects was better on Day 3 than on Days 2 and 4, but not significantly so (see Table 1).

The incidence of chest symptoms after GB was less than under resting conditions (4); only 1/10 subjects commented on an increased difficulty of breathing during the ride, and 5/10 found it easier on Day 3. Where "tightness in the chest" was noted, this did not appear for some 10 min after ceasing the ride (i.e. 25-30 min after the GB inhalation).

(c) Ventilatory measurements. The respiratory minute volume and carbon dioxide output 2½ - 4½ min after commencing the exercise on Day 5 were in the normal expected range for this rate of working (8). Both "test" and

"control" groups showed a significant reduction in the rate of working on Day 5 relative to performance on previous days. Parallel experiments, conducted over a five day period but without use of a Douglas bag on the fifth day have not shown this decrement of performance (7), and the effect observed in the present work can probably be attributed to the respiratory resistance offered by the mouthpiece, box-valve, and Douglas bag; although the added resistance is not great (~ 2 cm H_2O/l/sec at 85 l/min flow), the effect on "maximal" performance was greater than that of the GB inhalation.

2. Sub-maximal exercise tests

(a) Control values. Performance over the two week test period followed the general pattern previously described (7). There were no significant differences in any of the parameters measured between days 7 and 9, and control values have therefore been calculated as the mean of results on these two days.

(b) Effect of GB. The only change seen following inhalation of GB on Day 8 was a small increase of oxygen consumption relative to control values (+ 64 ± 32 ml STPD/min); this was of marginal significance ($0.05 < P < 0.1$). The group who inhaled isopropanol on Day 8 showed a decrease of oxygen consumption, perhaps due to anxiety, and the true extent of the change in oxygen consuption due to GB is thus given by the difference between the test (GB) group and the control (isopropanol) series; this difference is statistically significant ($\Delta = 98 \pm 42$ ml/min, $0.02 < P < 0.05$).

(c) Effect of isopropanol. Oxygen consumption and CO_2 output were decreased on Day 8, relative to control values. The ventilation was also significantly increased following exercise on the test day (extraventilation 5 - 15 min after exercise + 1.60 ± 0.74 l/min ATPS, relative to control values).

DISCUSSION

Little attention has previously been paid to quantitative aspects of physical working capacity during or following the inhalation of anti-cholinesterases. Vomiting has been described as a sequel of exercise in subjects given large percutaneous doses of GB (6). Exercise during chamber exposures to GB has also increased the "toxicity" of this agent to experimental animals (9), but this could be a secondary manifestation of (i) the larger dose of GB inhaled for a given ct with increase of respiratory minute volume, and (ii) changes in the rate and site of absorption with more rapid inhalation of the agent (5, 10). In the present work, variations of dose and rate or site of absorption with exercise were avoided, since the GB was given under standard conditions prior to the exercise. A decrease of maximum breathing capacity has also been described following inhalation of GB (11, 12); this probably represents a local effect of GB on airway resistance rather than a general decrease of muscular capacity.

The present work shows that moderate doses of GB have little influence on either the "maximal" rate of working or the performance of sub-maximal work tests. Objections to "maximal" work tests are well recognised. The level of achievement may depend to a considerable extent upon the motivation of the subjects, their personality, and attitude to the tests (7); however, psychologically "normal" individuals will perform one 5 min ride daily for 5 days without decrement of effort due to loss of motivation, and in both "test" and "control" series of the present group there was in general good agreement in the results for Days 2 and 4 (when no treatment was applied). Thus unless motivation was specifically disturbed by the treatment on Day 3, any change in the rate of working on Day 3 relative to Days 2 and 4 should be attributable to the treatment applied. The largest difference is obtained if the response of the "test" series Δ GB (-2.3 ± 1.8 watts) is compared with the response of the "control" series Δ isopropanol ($+ 1.9 \pm 1.3$ watts). Even calculated in this way, the difference in behaviour of "test" and "control" series (-4.2 ± 2.2 watts) is of marginal significance ($0.05 < P < 0.10$), and could easily be explained in terms of an increase

in the work of breathing due to bronchospasm, without postulating any more general alteration of muscular performance. Indeed, a similar reduction in the "maximal" rate of working is seen when using standard respiratory equipment such as a Douglas bag or a respirator.

The increase of oxygen consumption during the sub-maximal work tests can similarly be attributed to an increase in the work of breathing. The fact that this increase of oxygen consumption is achieved without a parallel increase of ventilation suggests that the inhalation of anticholinesterase may have increased the efficiency of gas transfer in the lungs. Some evidence in support of this view was found in earlier studies of carbon monoxide uptake following inhalation of GB (13).

With larger doses of GB, the work of breathing might be increased further by changes in lung and/or chest compliance, and alterations in the efficiency of the respiratory muscles. Reduction of cardiac output (14) would further limit transfer of oxygen from the lungs to the tissues, and peripheral effects such as accumulation of acetylcholine might reduce the mechanical efficiency of the leg muscles per se. However, present evidence (15, 16) suggests that none of these effects would be very important unless the dose was close to the lethal level; this is thus a hypothesis that cannot be tested experimentally in man.

The fact that local symptoms of anticholinesterase poisoning are less obvious when the mind of the subject is diverted by strenuous exercise is perhaps not surprising, but if the same is true of systemic symptoms, this would present an important obstacle to any scheme of therapy where part or all of the treatment was withheld until such symptoms appeared.

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(Sgd.) C. Lovatt Evans,
Head, Physiology Section.

RJS/DG

(Sgd.) W.S.S. Ladell,
Assistant Director (Medical).

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Performance on electrically-braked bicycle ergom[illegible]ser
in isopropanol (ipa) vapour immediately pr[illegible]ide

(a) "Test" series

Subject	Rate of work Day 1 watts	Rate of work Day 2 watts	Rate of work Day 3 (GB) watts	Rate of work Day 4 watts	Mean of 2 & 4 (control) watts	Δ GB watts
1	141	141	140	138	139.5	+ 0.5
2	162	148	142	142	145.0	- 3.0
3	183	174	173	177	[illegible]5.5	- 2.5
4	142	151	142	[illegible]6	153.5	- 11.5
5	157	154	143	159	156.5	- 13.5
[illegible]	162	161	165	164	162.5	+ 2.5
7	151	154	155	158	156.0	- 1.0
8	145	145	146	142	143.5	+ 2.5
9	162	160	162	158	159.0	+ 3.0
10	153	162	163	164	163.0	0.0
Mean ± S.E.	155.8 ± 4.0	155.0 ± 3.0	153.1 ± 3.8	155.8 ± 3.8	155.4 ± 3.4	- 2.3 ± 1.8

(b) "Control" series

Subject	Rate of work Day 1 watts	Rate of work Day 2 watts	Rate of work Day 3 (ipa) watts	Rate of work Day 4 watts	Mean of 2 & 4 (control) watts	Δ isopropenol watts
11	155	162	168	167	164.5	+ 3.5
12	155	155	159	155	155.0	+ 4.0
13	147	149	148	147	148.0	0.0
14	161	172	170	170	171.0	- 1.0
15	152	156	157	153	154.5	+ 2.5
16	152	158	156	169	163.5	- 7.5
17	152	155	155	148	151.5	+ 3.5
18	148	144	150	152	148.0	+ 2.0
19	156	149	162	159	154.0	+ 8.0
20	155	154	157	152	153.0	+ 4.0
Mean ± S.E.	153.3 ± 1.3	155.4 ± 2.4	158.2 ± 2.3	157.2 ± 2.7	156.3 ± 2.4	+ 1.9 ± 1.3

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TABLE 1

lly-braked bicycle ergometer. "Test" series received oral inhalation of GB (nominal dose 5 µg/kg) a) vapour immediately prior to third ride. "Control" series received isopropanol vapour alone

Rate of work Day 4 watts	Mean of 2 & 4 (control) watts	Δ GB watts	Rate of work Day 5 (Douglas bag) watts	Δ Douglas bag watts	Resp.min.vol. Day 5 l/min STPD	CO_2 output Day 5 l/min STPD	Comment after GB
138	139.5	+ 0.5	133	- 6.5	50.4	1.33	More determination needed.
142	145.0	- 3.0	138	- 7.0	51.1	1.57	Ride harder
177	175.5	- 2.5	172	- 3.5	73.8	2.43	Ride harder
156	153.5	- 11.5	157	+ 3.5	58.8	1.96	More out of breath
159	156.5	- 13.5	150	- 6.5	54.3	1.85	Ride harder
164	162.5	+ 2.5	162	- 0.5	47.8	2.18	Ride easier
158	156.0	- 1.0	147	- 9.0	56.9	1.47	Ride easier
142	143.5	+ 2.5	141	- 2.5	49.5	1.35	Ride easier
158	159.0	+ 3.0	162	+ 3.0	68.4	1.86	Ride easier
164	163.0	0.0	160	- 3.0	66.8	2.13	No difference
155.8 ± 3.8	155.4 ± 3.4	- 2.3 ± 1.8	152.2 ± 3.9	- 3.2 ± 1.3	58.8 ± 2.9	1.84 ± 0.12	

Rate of work Day 4 watts	Mean of 2 & 4 (control) watts	Δ isopropanol watts	Rate of work Day 5 (Douglas bag) watts	Δ Douglas bag watts	Resp.min.vol. Day 5 l/min STPD	CO_2 output Day 5 l/min STPD	Comment after isopropanol
167	164.5	+ 3.5	142	- 22.5	39.0	1.33	Spots before eyes, but ride easier.
155	155.0	+ 4.0	154	- 1.0	67.3	1.88	Less out of breath
147	148.0	0.0	144	- 4.0	72.8	1.72	Legs ache less
170	171.0	- 1.0	166	- 5.0	66.1	2.34	Less out of breath
153	154.5	+ 2.5	148	- 6.5	45.4	1.49	Legs ache less
169	163.5	- 7.5	152	- 11.5	58.4	1.82	Ride easier
148	151.5	+ 3.5	141	- 10.5	73.1	1.77	Legs weaker, but breathing easier.
152	148.0	+ 2.0	146	- 2.0	71.3	1.90	Legs ache more, but breathing easier.
159	154.0	+ 8.0	154	0	69.8	1.84	No difference
152	153.0	+ 4.0	150	- 3.0	60.9	1.78	Ride easier, but more out of breath.
157.2 ± 2.7	156.3 ± 2.4	+ 1.9 ± 1.3	149.7 ± 2.3	- 6.6 ± 2.1	62.4 ± 1.2	1.80 ± 0.08	

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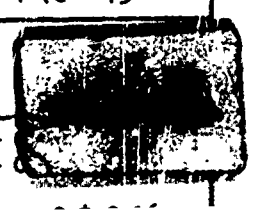
TABLE 2

Effects of GB (5 μg/kg single breath in isopropanol) and isopropanol alone on respiratory and cardiac cost of standard 15 min exercise (125 watts). Mean and S.E.

		Day 7 (control)	Day 8 (inhalation)	Day 9 (control)	Mean of 7 and 9	Δ 8
Oxygen consumption 15th min ex. (ml STPD/min)	GB	2213 ± 44	2258 ± 39	2176 ± 68	2194 ± 42	+ 64 ± 32 (*)
	IPA	2198 ± 66	2138 ± 63	2146 ± 107	2172 ± 66	- 34 ± 28
CO_2 output 15th min ex. (ml STPD/min	GB	2143 ± 60	2095 ± 41	1962 ± 48	2053 ± 36	+ 42 ± 23 (*)
	IPA	2015 ± 64	1950 ± 85	1997 ± 98	2006 ± 59	- 56 ± 27 *
Respiratory Quotient 15th min ex.	GB	0.97 ± 0.03	0.93 ± 0.02	0.91 ± 0.02	0.94 ± 0.02	- 0.01 ± 0.01
	IPA	0.92 ± 0.02	0.91 ± 0.02	0.95 ± 0.02	0.935± 0.02	- 0.025± 0.014
Respiratory minute volume 15th min ex. (l/min STPD)	GB	47.4 ± 1.9	46.9 ± 0.9	45.0 ± 1.1	46.2 ± 1.3	+ 0.7 ± 0.8
	IPA	47.4 ± 2.0	46.2 ± 3.1	45.0 ± 2.0	46.2 ± 1.6	- 0.0 ± 1.9
Ventilatory equiv. O_2 15th min ex. (l/100 ml)	GB	2.14 ± 0.08	2.08 ± 0.04	2.08 ± 0.05	2.11 ± 0.06	- 0.03 ± 0.02
	IPA	2.17 ± 0.09	2.15 ± 0.08	2.15 ± 0.08	2.16 ± 0.08	- 0.01 ± 0.02
Respiratory rate 15th min ex. (per min)	GB	26.2 ± 2.0	26.8 ± 1.6	27.3 ± 1.6	27.0 ± 1.6	- 0.2 ± 0.4
	IPA	24.6 ± 0.9	24.8 ± 1.6	25.8 ± 1.7	25.1 ± 1.2	- 0.6 ± 0.5
Tidal volume 15th min ex. (ml STPD)	GB	1885 ± 138	1808 ± 122	1690 ± 101	1788 ± 101	+ 20 ± 82
	IPA	1944 ± 83	1898 ± 121	1796 ± 103	1870 ± 89	+ 28 ± 75
Pulse total 0-5 min after exercise	GB	700 ± 14	670 ± 25	665 ± 18	687 ± 14	- 13 ± 12
	IPA	653 ± 32	674 ± 35	661 ± 32	658 ± 30	+ 16 ± 15
Pulse rate 15 min after exercise	GB	99 ± 3	98 ± 4	94 ± 3	97 ± 3	
	IPA	93 ± 6	97 ± 5	96 ± 5	95 ± 5	
Elevation of rectal temp, (°F) immediate	GB	0.63 ± 0.09	0.60 ± 0.10	0.74 ± 0.05	0.70 ± 0.09	-
	IPA	0.65 ± 0.13	0.59 ± 0.10	0.68 ± 0.06	0.67 ± 0.09	-
	GB	0.47 ± 0.10	0.49 ± 0.09	0.41 ± 0.06	0.48 ± 0.08	



Respiratory minute volume 15th min ex. (l/min STPD)	GB	47.4 ± 1.9	46.9 ± 0.9	45.0 ± 1.1	46.2 ± 1.3	+ 0.7 ± 0.8
	IPA	47.4 ± 2.0	46.4 ± 3.1	45.0 ± 2.0	46.2 ± 1.6	- 0.0 ± 1.9
Ventilatory equiv. O_2 15th min ex. (l/100 ml)	GB	2.14 ± 0.08	2.08 ± 0.04	2.08 ± 0.05	2.11 ± 0.06	- 0.03 ± 0.02
	IPA	2.17 ± 0.09	2.15 ± 0.08	2.15 ± 0.08	2.16 ± 0.08	- 0.01 ± 0.02
Respiratory rate 15th min ex. (per min)	GB	26.2 ± 2.0	26.8 ± 1.6	27.3 ± 1.6	27.0 ± 1.6	- 0.2 ± 0.4
	IPA	24.6 ± 0.9	24.8 ± 1.6	25.8 ± 1.7	25.4 ± 1.2	- 0.6 ± 0.5
Tidal volume 15th min ex. (ml STPD)	GB	1885 ± 138	1808 ± 122	1690 ± 101	1788 ± 101	+ 20 ± 32
	IPA	1944 ± 83	1893 ± 121	1796 ± 103	1870 ± 89	+ 28 ± 75
Pulse total 0-1 min after exercise	GB	700 ± 14	670 ± 25	665 ± 18	683 ± 14	- 13 ± 12
	IPA	653 ± 32	674 ± 35	661 ± 32	688 ± 30	+ 16 ± 15
Pulse rate 15 min after exercise	GB	99 ± 3	98 ± 4	94 ± 3	97 ± 3	+ 1 ± 3
	IPA	93 ± 6	97 ± 5	96 ± 5	95 ± 5	+ 2 ± 2
Elevation of rectal temp, (°F) immediate	GB	0.63 ± 0.09	0.60 ± 0.10	0.74 ± 0.05	0.70 ± 0.09	- 0.10 ± 0.11
	IPA	0.63 ± 0.13	0.59 ± 0.10	0.68 ± 0.06	0.67 ± 0.09	- 0.06 ± 0.11
15 min after ex.	GB	0.47 ± 0.10	0.49 ± 0.09	0.44 ± 0.06	0.49 ± 0.09	0 ± 0.06
	IPA	0.53 ± 0.12	0.55 ± 0.12	0.54 ± 0.06	0.55 ± 0.07	0 ± 0.08
Extravent. 0-1 min exercise	GB	17.0 ± 1.3	17.2 ± 1.0	18.8 ± 1.9	17.9 ± 1.4	- 0.7 ± 0.9
	IPA	17.4 ± 1.5	15.7 ± 1.7	18.7 ± 1.1	18.0 ± 1.2	- 2.3 ± 1.4
0-15 min exercise	GB	39.1 ± 1.7	38.1 ± 1.0	37.9 ± 0.9	38.5 ± 1.1	- 0.4 ± 0.3
	IPA	37.1 ± 1.6	38.5 ± 2.3	38.4 ± 2.1	37.8 ± 1.7	+ 0.7 ± 0.7
0-15 min after exercise (l/min ATPS)	GB	4.30 ± 0.28	4.32 ± 0.56	4.20 ± 0.51	4.25 ± 0.34	+ 0.07 ± 0.35
	IPA	3.79 ± 0.69	5.42 ± 1.15	3.85 ± 0.51	3.82 ± 0.55	+ 1.60 ± 0.74 *
Total Extravent. (l/ATPS)	GB	650 ± 26	627 ± 17	632 ± 18	641 ± 18	- 14 ± 15
	IPA	613 ± 31	663 ± 39	634 ± 35	623 ± 31	+ 40 ± 14 *
l/min/watt	GB	0.36 ± 0.03	0.34 ± 0.02	0.36 ± 0.03	0.35 ± 0.02	- 0.02 ± 0.01
	IPA	0.40 ± 0.03	0.44 ± 0.04	0.42 ± 0.04	0.41 ± 0.03	+ 0.03 ± 0.02

(*) Difference of marginal statistical significance.

* Difference statistically significant.

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